UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte JOHN M. POLO,
THOMAS W. DUBENSKY, ILYA FROLOV,
JASON P. GARDNER, GILLIS OTTEN,
SUSAN BARNETT, and DAVID A. DRIVER

Appeal No. 2006-2716
Application No. 09/551,977

ON BRIEF

Before SCHEINER, ADAMS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to alphaviruses capable of infecting human dendritic cells, which the examiner has rejected as based on an inadequate written description. We have jurisdiction under 35 U.S.C. § 134. We affirm.

Background

"Alphaviruses are a group of genetically, structurally, and serologically related arthropod-borne viruses." Specification, page 1. "Twenty-six known viruses and virus subtypes have been classified within the alphavirus genus." Id. "Sindbis virus is the prototype member of the Alphavirus genus." Id., page 2.

"Several members of the Alphavirus genus are being developed as expression vectors, including, for example, Sindbis virus. . . . The general strategy for construction of alphavirus-based expression vectors has been to substitute the viral structural protein genes with a heterologous gene. . . . RNA vectors having this configuration are self-amplifying, and are termed RNA 'replicons.'" Id., pages 3-4.

"One alphavirus, Venezuelan equine encephalitis virus, and its derived recombinant vector particles have been shown to be lymphotropic and infect murine dendritic cells. . . . However, no alphavirus or alphavirus variant was demonstrated to infect human dendritic cells, macrophages or antigen presenting cells." Id., page 4.

The specification discloses "isolated alphaviruses and recombinant alphavirus particles . . . which infect human dendritic cells." Id. Dendritic cells are antigen-presenting cells. Id., page 25. Targeting of dendritic cells with alphavirus vectors is said to "increase the potency of such alphavirus-based systems, particularly in the area of vaccines." Id.

The specification describes a working example in which Sindbis virus "was passaged 4 times in primary human dendritic cells obtained from different donors, with intermediate plaque purification in 293 and BHK-21 [i.e., non-dendritic] cells." Page 32, lines 9-16. "Following dendritic cell adaptation, a panel of plaque-purified clonal virus variants was able to grow efficiently in primary human dendritic cells." Id., page 33, lines 3-4. "One of the DC-selected [dendritic cell-selected] plaque-purified viruses was chosen for cDNA cloning . . . [and] designated SinDCchiron." Id., lines 7-13.

"In addition, a small number of spontaneous large plaque variants was observed sporadically. . . . [T]his large plaque virus variant was inefficient at infecting primary

human dendritic cells. . . . One of the large plaque variants was chosen for cDNA cloning, and . . . designated SinChironLP." Id., page 33, lines 15-25.

After the DNAs of the two virus clones were sequenced, only one amino acid difference was found: "This determinant for efficient infection of human dendritic cells . . . was located at E2 glycoprotein residue 160, with the strains containing the amino acids Gly or Glu, respectively." Id., page 37, lines 22-26. The E2 glycoprotein is a structural protein that protrudes from the surface of the virion. Id., page 2, lines 13-15.

The specification discloses that

> substitution of Gly for Glu at E2 160 alone is responsible for conferring the human DC-adapted phenotype. Additional amino acid substitutions, deletions or insertions at, or in close proximity to, this site can be readily generated by standard site-directed mutagenesis protocols, and when inserted into a full-length cDNA clone . . . , also may produce the same human DC adapted growth characteristics.

Page 37, line 27 to page 38, line 2.

Discussion

1. Claim construction

Claims 17, 19, and 21-23 are on appeal. The examiner has indicated that claim 20 is allowable. See the Appeal Brief, page 2 ("Claim 20 is allowable.") and the Examiner's Answer, page 2 (agreeing with the statement in the brief).

The claims have not been argued separately and therefore stand or fall together. See 37 CFR § 41.37(c)(1)(vii). Claim 17 is representative and reads as follows:

> 17. A recombinant alphavirus particle comprising
>
> an alphavirus replicon comprising a heterologous sequence; and
>
> an amino acid mutation in its E2 glycoprotein, wherein the mutation in the E2 glycoprotein is in the region corresponding to amino acids 158 – 162, numbered relative

to wild-type SIN E2 glycoprotein, and further wherein said particle is capable of infecting human dendritic cells, with the proviso that said recombinant alphavirus particle is not derived from ATCC # VR-2526.

Claim 17 is directed to a recombinant viral particle derived from any of the viruses of the alphavirus family except "ATCC # VR-2526," which is wild-type Sindbis virus (specification, page 31, line 3). The alphavirus replicon of the claimed viral particle comprises a heterologous sequence and a mutation in its E2 glycoprotein. Claim 17 specifies that the mutation is in the region of E2 corresponding to amino acids 158 to 162 of wild type "SIN." We understand "SIN" to refer to Sindbis virus; compare the specification at page 48, line 9 ("wild type SIN virus (e.g., ATCC# VR-2526")) with the specification at page 31, line 3 (VR-2526 is wild-type Sindbis virus).

The specification makes clear that claim 17 encompasses a variety of different mutations in the recited region of E2. See page 5, lines 4-8:

> Within certain embodiments . . . , the alphavirus or recombinant alphavirus particle has an amino acid substitution in the E2 glycoprotein as compared to wild-type, for example, at residue 158, 159, 160, 161, or, 162. . . . Within other embodiments, the alphavirus has an amino acid deletion or insertion in the E2 glycoprotein.

(Emphases added.)

We give claims their broadest reasonable interpretation consistent with the specification. See In re Morris, 127 F.3d 1048, 1054, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997). Therefore, we interpret claim 17 to encompass alphavirus replicons comprising a substitution, deletion, or insertion mutation in the E2 protein, in the region corresponding to amino acids 158 to 162 of the wild-type Sindbis virus E2 protein.

Claim 17 also includes a functional limitation: the alphavirus particle that comprises the mutated E2 protein must be capable of infecting human dendritic cells.

The specification defines "infects human dendritic cells" to mean that the viral particles "efficiently infect or transduce human dendritic cells." Page 19, line 19.

2. Written Description

Claims 17, 19, and 21-23 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking an adequate written description in the specification. The examiner acknowledges that the specification discloses a Sindbis virus mutant that infects human dendritic cells and has a specific mutation in amino acid 160 of the E2 protein. Examiner's Answer, page 3.

The examiner argues, however, that this mutant is not representative of the claimed genus of alphaviruses, for at least two reasons: (1) the alphavirus family comprises twenty-six known viruses (id.) and (2) the specification does not teach which amino acid substitutions at which positions among the amino acids corresponding to positions 158-162 of Sindbis E2 protein will likely result in an alphavirus gaining the ability to infect human dendritic cells (id., page 4, first full paragraph). The examiner concludes that, while the specification shows possession of the exemplified Sindbis virus mutant, it does not show possession of any other human dendritic cell-infecting alphaviruses having a mutation in the amino acids corresponding to 158-162 of the E2 protein. Id., page 3.

We agree with the examiner that the specification does not adequately describe the claimed genus of alphaviruses. Claim 17 is directed to alphavirus particles having, among other things, a mutation in the E2 protein, in the amino acids corresponding to 158 through 162 of wild-type Sindbis virus, where the mutation allows the virus particle to infect human dendritic cells. That is, claim 17 is directed to a subgenus of those

alphavirus particles having mutations in five specific amino acids of the E2 protein: claim 17 is limited to mutated viruses that have the ability to infect human dendritic cells.

"The 'written description' requirement . . . serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed." Capon v. Eshhar, 418 F.3d 1349, 1367, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005).

When a genus of DNAs is claimed, the genus may be described "by means of a recitation of a representative number of [the DNAs], defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

In addition to nucleotide sequence, representative species may be described by a combination of other characteristics: The "written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.'" Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 964, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002) (emphasis omitted, alterations in original).

"[W]hat is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability

of the aspect at issue, and other considerations appropriate to the subject matter."

Capon, 418 F.3d at 1359, 76 USPQ2d at 1085.

Describing the function of a genus of DNAs is generally not sufficient to meet the written description requirement: See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406:

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" . . . , without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function . . . does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Rather, "functional description can be sufficient only if there is also a structure-function relationship known to those of ordinary skill in the art." In re Wallach, 378 F.3d 1330, 1335, 71 USPQ2d 1939, 1943 (Fed. Cir. 2004).

Here, claim 17 is directed to a genus of mutant alphaviruses; i.e., mutant versions of any of the twenty-six viruses and virus subtypes classified as alphaviruses. The claimed genus is defined partly by structure, in that the mutants are required to have at least one mutation in one of five amino acids E2 glycoprotein (i.e., the amino acids corresponding to amino acids 158 through 162 of wild-type Sindbis virus E2 glycoprotein). The mutations can be insertions, deletions, and/or substitutions.

Claim 17, however, does not encompass all alphavirus mutants having at least one mutation in the specified amino acids. Claim 17 is limited to only those mutants in which the mutation changes the properties of the E2 glycoprotein in such a way that the

mutant alphavirus gains the ability to infect human dendritic cells. Thus, the genus of claimed alphavirus mutants is also defined partly by function.

The specification states that, at the time of filing, "no alphavirus or alphavirus variant was demonstrated to infect human dendritic cells, macrophages or antigen presenting cells." Page 4. Thus, claim 17 is not directed to E2 variants that maintain an activity possessed by wild-type E2, but to variants that have a new activity.

The specification discloses a single alphavirus mutant within the scope of the claims: a Sindbis virus variant with a substitution of glycine for glutamic acid at position 160 of the E2 glycoprotein. Page 37. The specification states that this substitution "alone is responsible for conferring the human DC-adapted phenotype." Id. The examiner has indicated that claim 20, which requires a mutation at the position corresponding to amino acid 160 of wild-type Sindbis virus E2 glycoprotein, is allowable.

Claim 17, however, does not require the mutant virus to include a mutation at position 160. The claim includes, for example, alphavirus mutants having an insertion, substitution or deletion at position 158 and no change at 160. That is, claim 17 does not require the only structural characteristic disclosed in the specification or in the art to confer the function that defines the claimed subgenus.

The specification discloses no blaze marks to direct those skilled in the art toward mutations at E2 positions 158, 159, 161, or 162 that are likely to confer the dendritic cell-infecting function that is conferred on alphaviruses by a Glu-to-Gly substitution at position 160. The specification, in fact, provides no evidence that the amino acids at positions 158, 159, 161, and 162 of E2 are involved in dendritic cell infection at all. See the sentence bridging pages 37 and 38: "Additional amino acid

substitutions, deletions or insertions at, or in close proximity to, [position 160] can be readily generated . . . and when inserted into a full-length cDNA clone . . ., also may produce the same human DC adapted growth characteristics."

The specification also makes clear that the knowledge in the art does not provide the description that is missing from the specification. See page 4 ("[N]o alphavirus or alphavirus variant was demonstrated to infect human dendritic cells.") and page 25 ("[T]he ability of an alphavirus to efficiently infect murine dendritic cells is not predictive of its ability to efficiently infect human dendritic cells.").

Whether a claimed genus is adequately described depends on, among other things, "the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue." Capon, 418 F.3d at 1359, 76 USPQ2d at 1085. Here, all of these factors weigh against the specification's single example being representative of the claimed genus. There was no knowledge in the field or in the prior art of E2 mutations that confer dendritic cell-infecting ability, the technology of conferring dendritic cell-infecting ability on alphavirus variants was brand new, and neither the prior art nor the specification provided any basis for predicting the effect of E2 mutations in amino acids other than 160 on the ability of an alphavirus variant to infect dendritic cells.

Describing a claimed genus in terms of its function is generally inadequate to comply with 35 U.S.C. § 112, first paragraph. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. Here, the specification purports to describe a functional subgenus of a structurally defined genus: those alphavirus mutants that have substitution, insertion, or deletion mutations at any of the amino acids corresponding to 158 through

162 of the E2 glycoprotein of wild-type Sindbis virus and that have the function of infecting human dendritic cells.

A "functional description can be sufficient only if there is also a structure-function relationship known to those of ordinary skill in the art." Wallach, 378 F.3d at 1335, 71 USPQ2d at 1943. The specification discloses one structure that corresponds to the recited function: a Glu-to-Gly substitution at amino acid 160. Claim 20, which requires a mutation at position 160, has been allowed. Appellants have described no other structure that corresponds to the recited function. We therefore agree with the examiner that the single disclosed species is not representative of the claimed genus. The rejection of claim 17 is affirmed. Claims 19 and 21-23 fall with claim 17.

Appellants argue that the claims are "drawn to the relatively small genus of recombinant alphavirus particles . . . , namely alphavirus particles that infect human dendritic cells and include a mutation in at least one of 5 specific amino acid residues in their E2 protein" (Br. 4). Appellants argue that the single mutant alphavirus disclosed in the specification is representative of the claimed genus because "Sindbis (the exemplified species) was considered to be the prototype for all alphaviruses" (id. at 6) and because the specification "describes production and use of recombinant alphavirus particles from various alphaviruses" (id. at 7).

This argument is unpersuasive. Regardless of the size of the claimed genus, the written description requirement is not met unless the specification describes the members of the claimed genus sufficiently to allow those skilled in the art to distinguish them from similar products that are not claimed. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406 (A fully described genus allows those in the art to "visualize or

recognize the identity of the members of the genus."). Here, the specification describes only a single compound that is encompassed by the claims, and does not provide a description of the other members of the genus that would show possession of the genus as a whole, at the time of filing, to those of skill in the art.

Appellants argue that their disclosure "demonstrate[s] possession of the claimed invention by clearly describing that which is new – mutations at residues 158-162 which impart DC-tropism" (id. at 8). We disagree. The specification shows only that Appellants were in possession of dendritic cell-infecting alphavirus mutants with a mutation at amino acid 160 of the E2 protein. The specification does not describe any mutations at amino acids 158, 159, 161 or 162 that confer the same activity. The examiner has indicated that claim 20, which requires a mutation at amino acid 160, is allowable. The examiner's decision accurately reflects Appellants' contribution to the field.

Appellants also argue that disclosure of a single species can satisfy the written description requirement, relying on Examples 9 and 14 of the training materials that accompanied the Written Description Examination Guidelines. Br. 9-13.

This argument is also unpersuasive. It is true that a single species can, in some cases, support a generic claim, but this is not one of those cases for the reasons discussed above. To the extent that Appellants rely on the cited examples as providing a substantive basis for their position, we note that the Guidelines and the examples that accompanied them do not have the force and effect of law. See 66 Fed. Reg. 1099, 1104 (Jan. 5, 2001) ("This revision [of the earlier Interim Guidelines] does not constitute substantive rulemaking and hence does not have the force and effect of law."). The

Guidelines and examples represent the USPTO's interpretation of the controlling case law that existed at the time they were prepared. See id. at 1099. As discussed above, in this case we interpret the controlling case law to support the examiner's rejection.

Appellants also argue that the examiner did not properly consider the declaratory evidence they submitted to support their position. Br. 13-15. According to Appellants, the Polo declaration is "directly applicable to a written description inquiry in that it clearly demonstrates that Appellants were in possession of the claimed invention at the time of filing" (id. at 15).

This argument is unpersuasive. The Polo declaration is limited to the issue of enablement; i.e., whether practicing the full scope of the claims would have required undue experimentation. The declaration provides no evidence to show that those skilled in the art would have considered Appellants to be in possession of the claimed genus of alphavirus mutants based on the single disclosed species.

Enablement and written description are separate requirements of 35 U.S.C. § 112, first paragraph. See Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991):

> 35 U.S.C. 112, first paragraph, requires a "written description of the invention" which is separate and distinct from the enablement requirement. The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed.

See also University of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 921, 69 USPQ2d 1886, 1895 (Fed. Cir. 2004) ("[A]n invention may be described without an

enabling disclosure of how to make and use it. . . . Moreover, an invention may be enabled even though it has not been described.").

We agree with the examiner that the Polo declaration is entitled to little if any weight as evidence that those of skill in the art would have considered the specification's description adequate to show possession of the genus defined by claim 17. The examiner correctly concluded that the declaratory evidence does not overcome the rejection.

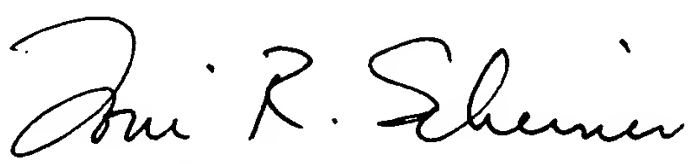
Finally, Appellants argue that their "specification contains express support for the claimed invention and, accordingly, possession of the invention at the time the application was filed has been established." Reply Brief, page 8. This position has been squarely rejected by the Federal Circuit. See Enzo, 323 F.3d at 969-70, 63 USPQ2d at 1616: "If a purported description of an invention does not meet the requirements of the statute, the fact that it appears as an original claim or in the specification does not save it. A claim does not become more descriptive by its repetition, or its longevity."

Summary

The evidence of record shows that those of skill in the art would not have considered the single species disclosed by the specification to be representative of, and to show possession of, the genus of alphavirus particles defined by claim 17. We therefore affirm the rejection for lack of adequate written description. Claims 19 and 21-23 fall with claim 17.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED



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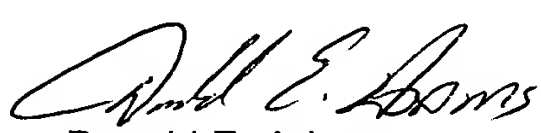
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